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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,933	06/13/2005	Jan Koek	26782U	5995
34375	7590	02/29/2008	EXAMINER	
NATH & ASSOCIATES PLLC 112 South West Street Alexandria, VA 22314				DESAI, RITA J
ART UNIT		PAPER NUMBER		
1625				
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02/29/2008		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,933	KOEK ET AL.	
	Examiner	Art Unit	
	Rita J. Desai	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 29 November 2007.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 3-6 and 8 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 3-6 and 8 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Claims pending 3-6 and 8 are pending.

The rejection of claims 1-6 and 8 .

The rejection of the claims 1-6 and 8 under 35 USC 102 (b) over WO 01/72756 , WO 01/72754 and WO 98/42707 has been withdrawn as applicants have amended the claims to specific species and the prior art is to a genus.

However the rejection of the claims 3-5 and 8 stand rejected under 35 USC 103 over WO'757, WO'754 and WO' 707 .

Applicants arguments and declaration are not found to be persuasive. The use of different silyl protecting groups is obvious and the results not unexpected.

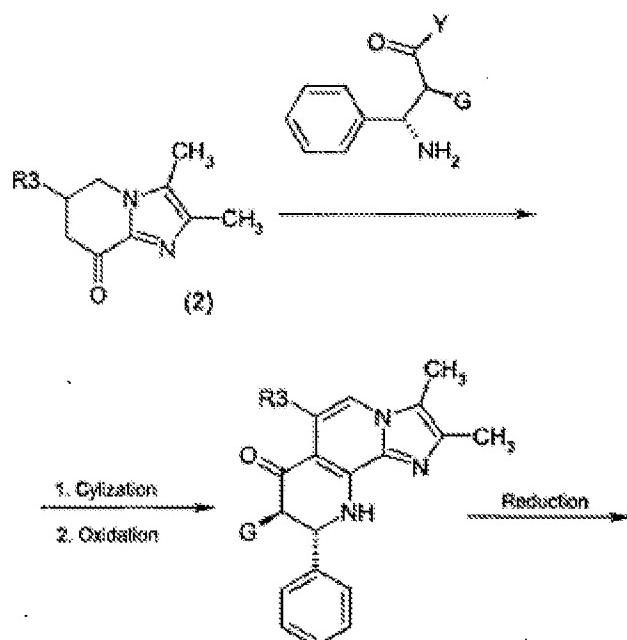
The compound claims just differ in the type of Si protecting groups.

The process of claim 8 is the same as that given in "707 except for the protecting group.

WO '754 discloses the process

Scheme 2

In the scheme below, the preparation of compounds of the form $\text{CH}_2\text{R}^4\text{a}$ or R^4b = hydroxyl and $\text{X} = \text{NH}$ starting from compound 1) is outlined by way of example:



G in the reference is defined as a Silyl protecting group. See page 26 and

suitable leaving group, for example a methoxy group. The group G – depending on whether the compound where R^5a and R^5b = hydrogen or whether a compound where R^5a or R^5b hydroxyl is desired – is either hydrogen or a hydroxyl group (for example protected by a silyl silyl radical).

Applicants argue that the examiner does not have any references to indicate that any other Silyl group could be used.

The 1972 reference also teaches the Si protecting groups and some of the advantages and uses of the t-butyldimethylsilyl groups. Corey et al 1972

Journal of the American Chemical Society / 94:17 / August 23, 1972

See below.

i-

Another key discovery was that dimethyl-*tert*-butylsilyl ethers are cleaved rapidly to alcohols by treatment with 2–3 equiv of tetra-*n*-butylammonium fluoride in tetrahydrofuran at 25°.⁸ Further, dimethyl-*tert*-butylsilyl ethers may be converted to alcohols under acidic conditions (e.g., in 2:1 acetic acid–water at 25°) at a rate comparable to that for the cleavage of tetrahydropyranyl ethers.

Dimethyl-*tert*-butylsilyl ethers are stable to aqueous or alcoholic base under the normal conditions for acetate saponification, and are also stable to hydrogenolysis⁴ (H_2 –Pd) and mild chemical reduction (e.g., Zn–CH₃OH). Consequently, such protection can be used, for instance, in the case of a hexahydroxy compound with hydroxyl groups 1–6 protected as: 1, acetate; 2, β,β,β -trichloroethyl ether; 3, benzyl ether; 4, dimethyl-*tert*-butylsilyl ether; 5, tetrahydropyranyl ether; and 6, methyl ether. For this case the unmasking of hydroxyls can be conducted in a number of ways including the following: (a) groups 1–6 may be unmasked in that order by the reagents K CO CH OH

The Silicon-Bonded Groups discloses a variety of Silyl groups. Amongst them are the ones used by the applicant. In the art of synthesis and with functional groups, it is routine to change protective groups for optimization. It is within the scope of routine experimentation.

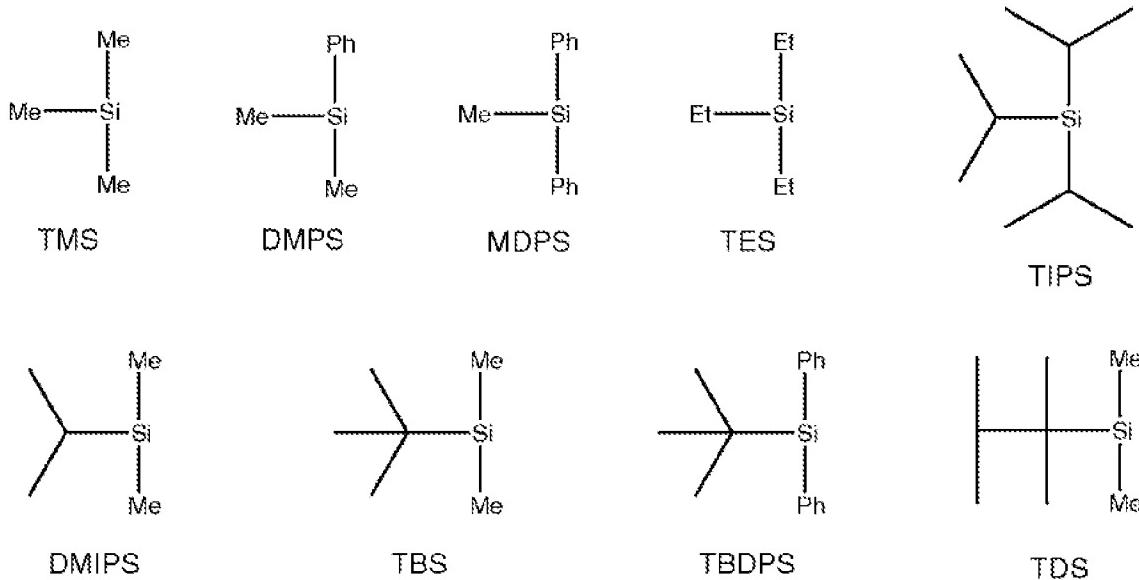
See page 4 of the reference Silicon Blocking agents , Gelest Inc co-op, catalog, 2004, used for synthesis and protection and derivitazion.

+ SILICON-BASED BLOCKING AGENTS

General Considerations

The ideal protecting group for an active-hydrogen moiety such as an alcohol or amine would be one that would mimic the hydrogen atom itself, but be much more flexible in its reactivity. It would readily go on in high yield, be stable over as wide a variety of reaction conditions as possible and, at the same time, be selectively removable in the presence of other functional groups including other protecting groups. While no single silyl group can fulfill all of these conditions in all cases, the available range of silicon-based blocking agents can offer the synthetic chemist viable answers to nearly every protection-deprotection challenge. The ability to vary the organic groups on silicon introduces the potential to alter the R_3Si group in terms of both its steric and electronic characteristics and thereby influence the stability of the silylated species to a wide variety of reaction and deprotection conditions. This allows the synthetic chemist to select a silyl protecting group that can, for example, be simultaneously removed during the work-up of the reaction step(s) that required the protection, or that can be selectively removed in the presence of another silyl or other protecting group.

In addition to having the ability to be fine-tuned to fit a particular need, the ease and high-yield introduction and deprotection of the silyl protecting groups contribute significantly to their popularity and utility. The commonly utilized trisubstituted silyl protecting groups and their acronyms are shown below.



It should be noted that TBS here is the tert-butyl dimethyl silyl (TBDMS)

Thus the TMS of the prior art has been replaced by the TBS (same as the TBDMS).

The reference further teaches the stability of the protecting groups under different conditions.

Stability of Silyl-Protected Functional Groups

The relative stabilities of the silyl-protected functional groups, for example, alcohols as silyl ethers, is roughly the same as the relative rates for their introduction. It must be remembered, however, that the stability of the system is dependent upon the specific reaction conditions and, in particular, the pH. For example, phenyl-substituted silyl ethers are equal or more reactive than their trimethylsilyl counterparts under alkaline conditions, but less reactive under acidic conditions. In general terms, however, the relative stabilities of the silyl-protected functional groups will follow the order of: $\text{^1Pr}_3\text{Si} > \text{^1PhMe}_2\text{Si} > \text{^1BuPh}_2\text{Si} > \text{^1BuMe}_2\text{Si} > \text{^1PrMe}_2\text{Si} > \text{Et}_3\text{Si} > \text{Ph}_2\text{MeSi} > \text{Me}_3\text{Si}$. Again, this order is meant to be a general guide as the actual stabilities will depend on the pH of the medium as well as other reaction conditions. The results of a study of the stability of various silyl ethers as a function of the groups on silicon and the nature of the alcohol towards various hydrolysis conditions and common organic reagents are shown in **Table 1**. The reader is referred to the excellent review by Crouch and Nelson on the selective deprotection of silyl groups in synthesis.⁹

Examiner has provided pre and post filing references that it is routine experimentation to optimize conditions, change the protecting groups to obtain better yields depending upon the reaction conditions.

Thus to a person skill in the art and in the field of synthesizing compounds would have found it obvious to interchange and obvious to try the various silyl protecting groups depending on the reaction condition, to optimize the reaction.

The various WO documents clearly each several modifications of the process of making the compounds of formula I.

According to KSR International Co. v Teleflex inc. et al., April 30 2007., there are several rationales for obviousness.

Rationales

- (A) Combining prior art elements according to known methods to yield predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (E) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;
- (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;
- (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

In this case all the elements are known.

The process, compounds are known in the prior art, the process and the use of Silyl protecting groups is also known. The motivation to optimize the reaction conditions is also there, so it would be obvious for one of skill in the art to change the Silyl groups to obtain the process and the compounds of this invention. Thus meeting the rational of obvious to try, choosing from a finite number of identified, predictable solutions, with a reasonable expectation of predictable results.

Thus the rejection still stands.

Conclusion

Claims 3-6 and 8 are not found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 1625

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Rita J. Desai
Primary Examiner
Art Unit 1625

R.D.
February 16, 2008

/Rita J. Desai/
Primary Examiner, Art Unit 1625